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EXAMINER	
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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,060	ARTAVANIS-TSAKONAS ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,91-106,108 and 113-116* is/are pending in the application.

4a) Of the above claim(s) *101-106,108-111,113,114 and 116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,91-100,115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. The amendment filed on 11 February 2008 has been entered into the record and has been fully considered. Claims 34, 94-96 and 106 are amended. Claims 90, 107 and 112 have been canceled.

2. Claims 106, 109 and 110 are amended to recite the non-elected species (Delta, Serrate protein – see Applicant's response to restriction requirement dated 9/29/06 and 6/14/07). Hence claims 106, 109 and 110 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim.

3. **The restriction requirement is still deemed proper and is therefore made FINAL.**

4. Claims 34, 91-100 and 115, drawn to a method of treatment of a disease using an antagonist to Notch proteins, are being considered for examination in the instant application.

5. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

6. Applicant's arguments filed on 11 February 2008 have been fully considered. New grounds of objection and rejection are as follows:

Correction of Inventorship (1.48(b))

7. In view of the papers filed 11 February 2008, the inventorship in this nonprovisional application has been changed by the deletion of Richard Grant Fehon and Christine Marie Blaumueller. The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Response to Amendment

Withdrawn objections and/or rejections

8. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (11 February 2008).

9. Upon claim amendments and Applicant's persuasive arguments, rejection of claims under 35 U.S.C. § 112, second paragraph is withdrawn.

Claim rejections/objections maintained

Objection to Specification

10. Applicant's amendment dated 11 February 2008, updating the first paragraph of the specification is acknowledged. However, the amendment has typographical errors as follows:

A statement reading "...09/564,504 filed May 4 **2000** (not 2002), now abandoned, which is a divisional of application Serial No. 08/532,384 filed September 22, 1995, now U.S. Patent No. 6,083,**904** (not 6,083,590)....." should be entered (correct information in bold).

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. The rejection of claims 34, 96, 106, 107, under 35 U.S.C. 102(e) as anticipated by Yamada et al. US Patent No 5211657, filed on 7 November 1988, is applied to amended claims 34 for reasons of record in the Office Action dated 9 August 2007.

12. Claim 34 is directed to a method of treating a disease in a subject characterized by increased expression or activity or a Notch protein or Notch derivative, comprising the administration of a molecule such as an anti-Notch antibody, capable of binding a Notch protein or a Notch derivative.

13. Applicant alleges that the Examiner has "mistakenly characterized the teachings of Yamada" because Yamada et al teach synthetic peptides having laminin activity and antibodies generated thereof that can be used for the treatment of diseases, but do not teach antibodies to laminin A. Based on the BLAST sequence comparisons between the synthetic peptides of Yamada et al. and human Notch 1, Notch 2, Applicants demonstrate the absence of homology between the said sequences. Applicants conclude that antibodies generated to the peptides of the reference cannot be expected to cross-react with the mammalian Notch protein and, thus, cannot anticipate the antibody or the method using the antibody of the instant invention. Applicant, therefore, requests the rejection to be withdrawn.

14. Applicant's arguments are fully considered but are found to be persuasive in part. The Office agrees that Yamada et al. teach synthetic peptides to laminin A and antibodies generated to these peptides. The Office also agrees with the results presented in Exhibits A and B by Applicant showing the lack of homology between Notch 1/Notch 2 proteins and Yamada et al's peptides. However, by current amendment of claim 34, Applicant claims the method of treating a disease by administering an anti-Notch antibody capable of binding to a Notch protein or a **Notch derivative** (emphasis added). The instant specification defines Notch protein derivatives as peptides that can be made by altering the Notch peptide sequence by addition, deletion or substitution of amino acids, by various methods including chemical synthesis (para 0169, 0173). Furthermore,

the specification teaches that therapeutics comprise Notch protein derivatives comprising one or more EGF like repeats of the Notch protein (para 0178), and as evidenced by Jang et al. (Curr Opin Mol Ther 2: 55-65 – provided in the IDS), Notch antagonists including antibodies consist of EGF like repeats (page 60, col 1, para 3). Turning over to Yamada et al, the reference teaches antibodies generated to synthetic peptides derived from the deduced amino acid sequence of the laminin A chain, that can be used for the treatment of diseases like cancer (abstract, col 3, para 3, Table III). Additionally as stated in the previous Office Action, the reference also teaches that the laminin A chain has sequence homology with several EGF-like repeats, exhibiting an optimized augment score of 320 (based on FASTA program) with Notch protein. Furthermore, Yamada et al teach pharmaceutical compositions comprising therapeutically effective amounts of the antibody, which can be clinically useful for blocking the tumor growth activity of laminin. Because of the differences in the amino acid sequences between the native Notch proteins and their derivatives, and because Applicants did not specifically compare the Notch derivative sequences of the instant claim with the synthetic peptides of the reference, antibodies to Yamada et al's peptides would anticipate the claimed antibodies and methods using the same, absent evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The rejection of claims 95, 97-99, and 109-110, under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. US Patent No 5211657, filed on 7 November 1988, in view of Harlow and Lane (Cold Spring Harbor Laboratory, 1988), is applied to amended claims 95, 97-99 for reasons of record in the Office Action dated 9 August 2007.

16. Applicant argues that since the primary reference of Yamada et al. do not teach the antibodies to a Notch protein as explained above, Harlow does not remedy the deficiencies of Yamada et al, and therefore, cannot render the claimed method obvious.

17. As stated above, although Yamada et al do not teach antibodies to a Notch protein, the reference teaches antibodies to synthetic peptides derived from the deduced amino acid sequence of the laminin A chain that can be used as a therapeutic for treatment of tumors. Additionally, as stated above the amended claims recite antibodies to a "Notch derivative". Because of the similarities in the amino acid domains of laminin and the Notch proteins, especially in the EGF repeat containing domains as explained above, and

because Applicant did not provide evidence for the contrary, the antibodies to these sequences can cross-react with Notch protein/derivative and can render the claimed method obvious.

18. Thus, the claimed invention as a whole was prima facie obvious over the combined teachings of the prior art.

35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. The rejection of claims 34, 90-100, 106-107, 109-110 and 115, under 35 U.S.C. 112, first paragraph, is applied to amended claims 34, 91-100 and 115, because the specification, while being enabling for a method of reducing tumor growth in mice, using an antibody to synthetic peptides derived from laminin A chain, and a method for reducing the expression of Notch protein in tumor tissue in vitro and in vivo, does not reasonably provide enablement for a method of treating any disease such as malignancy in humans, by administering any molecule or an antibody/portion of the antibody that can antagonize or bind to any Notch protein or its derivative.

20. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art,

the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

21. The claims are drawn to a method of treating any disease, comprising administration to a subject (human), a molecule that antagonizes Notch protein function such as intracellular signal transduction, wherein the molecule is an anti-Notch antibody to a Notch protein/Notch derivative, wherein the antibody is a neutralizing monoclonal antibody (claims 34, 95-99, 115). The claims also recite that the disease is malignancy (cervical, breast, colon, melanoma, seminoma, etc.), characterized by increased activity or expression of Notch protein or its derivative (claims 34, 91-94). The claims further recite that the antibody only binds to human Notch and not to the Drosophila protein (claim 100).

22. Applicant alleges that the rejection is in error because the "specification provides considerable guidance and direction to practice the claimed invention without undue experimentation". Applicant argues by citing paragraphs from the specification showing the diagnostic and therapeutic/prophylactic uses of Notch protein antagonists, and asserts that a sound scientific reasoning for a molecular basis of the antagonist or an anti-Notch antibody as a cancer therapeutic is presented. Applicant further supports this contention by providing several post art references demonstrating the use of antagonist/antibodies to Notch or its proteolytic enzyme γ-secretase in malignancy. Furthermore, Applicants refute the

Jain reference by asserting that it provides information on solid tumors only, while Notch signaling encompasses both "solid and non-solid tumors". Applicants, therefore, conclude that "based upon the teaching of the present specification regarding Notch and malignancy", the common knowledge about antibodies in general, and the production of anti-Notch antibodies in particular, a skilled artisan would "clearly understand the molecular basis for the use of an anti-Notch antibody as a therapeutic for treating malignancy". Because the "specification provides a reasonable amount of guidance and direction to the experimentation", Applicants assert that the required experimentation may be routine, not undue. Lastly, Applicants request clarification of the sentence in the last Office Action (para 18), which reads, "It is noted that the Examiner has interpreted Notch derivatives or fragments, including those comprising EGF repeats", with respect to Examiner's interpretation of the Notch derivatives or fragments.

23. Applicant's arguments have been fully considered but have not been found to be persuasive. At the onset, to clarify Applicant's query regarding the sentence in para 18, it is noted (as stated above) that the claims are drawn to a method of treating a disease by administering an anti-Notch antibody capable of binding to a Notch protein or a Notch derivative (emphasis added). The instant specification defines Notch protein derivatives as peptides that can be made by altering the Notch peptide sequence by addition, deletion or substitution of amino acids, by various methods including chemical synthesis (para 0169, 0173).

Furthermore, the specification teaches that therapeutics comprise Notch protein derivatives comprising one or more EGF like repeats of the Notch protein (para 0178). Therefore, based on the instant specification's definition, the Office broadly interprets a "Notch derivative" of the claims as that which would encompass sequences or fragments deduced from Notch protein including amino acid sequences comprising EGF like repeats.

24. With regards to Applicant's arguments on sufficient guidance to make and use the claimed invention provided in the specification, it is admitted that there exists a correlation of increased Notch expression in tumor tissue versus normal tissue in humans and other mammals. That Notch is expressed at a higher level in malignant tissue than in the corresponding non-cancerous tissue is not disputed by the examiner. Moreover, that one can manufacture an anti-Notch antibody is also not in dispute. The examiner agrees that Notch plays a fundamental role in the differentiation of uncommitted cells. However, the instant specification does not provide any objective guidance or working examples for the treatment of diseases like cancer, in humans by administering any molecule or an antibody to a Notch protein or its derivative. The specification does not support that which is claimed since the disclosure is fundamentally devoid of any description, which would enable one of ordinary skill in the art at the time to practice the invention with an expectation of success. On the contrary, the specification merely prophetically claims to treating malignancy (known or suspected), which does not enable the skilled artisan to treat a human with a

complex disease like cancer with predictability and success. The claimed antagonist/antibody must provide some sort of prophylactic or therapeutic effect for patients. Undue experimentation would still be required to derive at predictable results.

25. Undue experimentation would also be required of a skilled artisan to make antibodies to the innumerable Notch derivatives and treat diseases like cancer with a reasonable amount of success using the same. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein, which are tolerant to change, and the nature and extent of changes that can be made in these positions. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology

15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

26. The relevant art cited by the Applicant does not add to the pertinent information to undo the discrepancy in the specification. The art (Applicant cited) teaches monoclonal antibodies to Notch protein (Li et al), inactivation of increased expression of Notch 3 in cancer cell lines in vitro induced by small interfering RNA and γ-secretase inhibitors (Park et al., Konishi et al., Farnie (I) et al.), inhibition of differentiation of mammary cells in culture using γ-secretase inhibitors (Dontu et al,), and prolonged survival of mice implanted with glioma cells treated with Notch1 small interfering RNA as opposed to mice implanted with control glioma cells (Purow et al) (references included in the IDS). However, the relevant art does not provide any information on the treatment of cancer or other diseases by the administration of an antibody to Notch protein or its derivative into a human. As stated in the previous Office Action, although Notch plays a role in neoplastic cell transformation, N1 (Notch1) can also function as a tumor suppressor in the skin of mouse (Koch et al. Cell Mol Life Sc 64: 2746-2762, 2007; pages 2753-2754). Conflicting results of Notch expression are also observed in tumor samples. For example, Hayashi et al (see IDS) teach the absence of Notch1 expression in seminoma tissue.

However, the art acknowledges that many aspects of Notch signaling are poorly understood, because of the "overlapping versus distinct functions in a given developmental context" (Harper et al page 469, last para). Also unknown are the differences in Notch signaling in a physiological Vs malignant state. The presence of different Notch isoforms in different cancers, their individual effects and the functional relationship between each of the isoforms add to the

complexity of the signaling pathway. Notch induced transformation is further confounded by the fact that different Notch receptors are involved in different stages of tumor progression, and the receptors are shown to function as downstream mediators of each other.

However, the instant specification and relevant art fails to provide any evidence to demonstrate treatment of any disease or cancer by administration of an antagonist or antibody to Notch protein or its derivative to a human subject. Absent evidence to the contrary, the method is only enabled for reducing tumor growth by administration of antibody to Notch sequence fragments/derivatives having EGF repeats, such as Laminin. Furthermore, with regards to the generally treatment of cancer with antibodies, the specification lacks working examples, and the nature of the invention is unpredictable.

27. Additionally, Applicant's comments with respect to the Jain reference are irrelevant as the claims are inherently directed to solid tumors (cervical, breast, colon, melanoma, and lung). Since the claims do not recite explicitly or implicitly non-solid tumors, Applicant's argument is moot. In conclusion the claimed treatment of diseases or cancer by administering an anti-Notch antibody to a Notch protein or derivative is unpredictable in the absence of support provided by the specification for the following reasons: (1) The antibody may be inactivated before producing an effect, e.g. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) The antibody may otherwise not reach the target area because, for example, (a) the protein may not be able to cross the mucosa, (b) the antibody may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect, and (c)

circulation to or in the target area may be insufficient to carry the drug; (3) A large enough effective local concentration may not be capable of being established. The claims are based on pure speculation that the method and/or compositions would be effective. While data obtained from in vitro assays are useful in screening for potentially useful therapeutic agents, one cannot simply extrapolate the data to an in vivo system. The success of the claimed method is dependent on adequate concentrations of drug reaching the desired site in vivo. There are many properties of antibodies such as deactivation by the liver, binding to plasma proteins, rapid excretion, etc. that cannot be ascertained by in vitro experiments. No guidelines are presented in the specification, which would aid one of skilled in the art in selecting parameters for successful practice of the method.

28. Specifically a proper analysis of the Wands factors was provided in the last Office Action. Due to the large quantity of experimentation necessary for treating any disease or treating cancer by administration of an antibody to a Notch protein or its derivatives, to a human; the lack of direction/guidance presented in the specification; the complex nature of the invention; the unpredictability of successful treatment of complex diseases like cancer; the unpredictability of therapeutics involving antibodies; and the breadth of the claims which fail to recite antibodies to specific Notch proteins or derivatives consisting of specific regions of Notch proteins, undue experimentation would be required of the skilled artisan to practice the instant invention, as currently claimed.

35 USC § 112-Written description

29. The rejection of claims 34, 90-100, 106-107, 109,-110 and 115 under 35 U.S.C. 112, first paragraph, is applied to claims 34, 91-100 and 115, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

30. The claims are drawn to a method of treating any disease, comprising administration to a subject (human), a molecule that antagonizes Notch protein function such as intracellular signal transduction, wherein the molecule is an anti-Notch antibody to a Notch protein/Notch derivative, wherein the antibody is a neutralizing monoclonal antibody (claims 34, 95-99, 115). The claims also recite that the disease is malignancy (cervical, breast, colon, melanoma, seminoma, etc.), characterized by increased activity or expression of Notch protein or its derivative (claims 34, 91-94). The claims further recite that the antibody only binds to human Notch and not to the Drosophila protein (claim 100).

31. Applicant argues that the claimed subject matter is described by the specification as per 35 U.S.C. 112, first paragraph guidelines. Specifically, Applicant asserts that since Notch proteins are well characterized in the art as well as the instant specification, and since the functional and structural characteristics of antibodies and fragments thereof are well known, an antibody

to the Notch protein meets the written description requirements of Section 112. Applicant recites case laws in support of this contention.

32. Applicant's arguments are fully considered, however, are not found to be persuasive. As stated above, Examiner admits that Notch protein is well characterized, and antibodies can be made to such well-known proteins. However, the instant claims are drawn to a method of using any molecule or an antibody that antagonizes Notch function, for treating a disease or treating cancer. Furthermore, the instant specification speculates the administration of single-stranded DNA antisense Notch oligonucleotides to cancer patients that express Notch RNA (Section 5.5.2, pages 35-36). However, the brief description in the specification describing antibodies to human Notch homologs hN and TAN-1, or Notch antisense nucleic acid, does not comprise a representative number of species of antibodies to any Notch protein or Notch derivative, or a representative number of species of molecules for antagonizing the function of a mammalian Notch protein, to be used for administration in humans for cancer treatment, hence does not comprise an adequate written description of a genus of antibodies to the genus of Notch proteins or to a genus of Notch derivatives thereof, or to a genus of Notch protein antagonizing molecules, and methods using such. Contrary to Applicant's assertion, the specification has not shown a relationship between the structure, function, or properties of the antibodies or antagonist molecules to the claimed genus of Notch proteins and its derivatives. As stated in the previous Office Action, the skilled artisan cannot envision the

entire genus of Notch proteins, its derivative, antibodies, and molecules antagonizing the Notch function, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. Therefore, only antibodies to hN and TAN-1, Notch antisense nucleic acid, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

New Rejection

35 USC § 112, first paragraph-New Matter

33. Claims 34, 91-100 and 115, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

34. The claims are drawn to a method of treating a disease, comprising administration to a subject (human), a molecule that antagonizes Notch protein function such as intracellular signal transduction, wherein the molecule is an anti-Notch antibody to a Notch protein/Notch derivative, wherein the antibody is a neutralizing monoclonal antibody (claims 34, 95-99, 115). The claims also recite

that the disease is malignancy (cervical, breast, colon, melanoma, seminoma, etc.), characterized by increased activity or expression of Notch protein or its derivative (claims 34, 91-94). The claims further recite that the antibody only binds to human Notch and not to the Drosophila protein (claim 100).

35. The specification as originally filed does not provide adequate written description for reciting "malignancy characterized by ...increased expression of ...a Notch derivative", because the specification does not contemplate the narrowed limitation, for malignancy being characterized by increased expression of a Notch derivative. These are not expressly asserted, nor do they flow naturally from the specification. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06.

Conclusion

36. No claims are allowed.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is 571-272-90379037. The examiner can normally be reached on M-F.

38. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911. The fax phone number for the organization where this application or

proceeding is assigned is 571-273-8300.

39. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
3 May 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649